Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients†

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Aims
To assess the effects of multi-disciplinary cardiac rehabilitation (CR) on survival in the full population of patients with an acute coronary syndrome (ACS) and patients that underwent coronary revascularization and/or heart valve surgery.

Methods and results
Population-based cohort study in the Netherlands using insurance claims database covering ~22% of the Dutch population (3.3 million persons). All patients with an ACS with or without ST elevation, and patients who underwent coronary revascularization and/or valve surgery in the period 2007–10 were included. Patients were categorized as having received CR when an insurance claim for CR was made within the first 180 days after the cardiac event or revascularization. The primary outcome was survival time from the inclusion date, limited to a total follow-up period of 4 years, with a minimum of 180 days. Propensity score weighting was used to control for confounding by indication. Among 35 919 patients with an ACS and/or coronary revascularization or valve surgery, 11 014 (30.7%) received CR. After propensity score weighting, the adjusted hazard ratio (HR) associated with receiving CR was 0.65 (95% CI 0.56–0.77). The largest benefit was observed for patients who underwent coronary artery bypass grafting (CABG) and/or valve surgery (HR = 0.55, 95% CI 0.42–0.74).

Conclusion
In a large and representative community cohort of Dutch patients with an ACS and/or intervention, CR was associated with a substantial survival benefit up to 4 years. This survival benefit was present regardless of age, type of diagnosis, and type of intervention.

Keywords
Cardiac rehabilitation • Coronary artery disease • Acute coronary syndrome • Survival • Outcomes research • Observational study

Introduction

Millions of deaths due to cardiovascular disease (CVD) can be prevented, with cardiac rehabilitation being one of several recommended treatments. Specifically, international guidelines recommend cardiac rehabilitation (CR) for all patients with an acute coronary syndrome [ACS; acute myocardial infarction (MI) or unstable angina pectoris], and for those who have undergone coronary revascularization [coronary artery bypass graft surgery (CABG) or percutaneous coronary interventions (PCI)], or valvular surgery. Nevertheless, CR uptake remains low.

Recently, the American Heart Association suggested that a lack of knowledge about the benefits of outpatient CR among both patients and healthcare providers is a major contributor to its persistent
underutilization and stressed the need for research initiatives to fill gaps in the CR literature. Although the efficacy of CR has been studied in at least 47 separate randomized controlled trials (RCTs),11,12 most of these studies were performed in the 1980s and 90s. After this period, treatment options for coronary artery disease have been improved substantially [e.g. by the introduction of primary PCI and the implantable cardioverter defibrillator (ICD)]. Therefore, it has been questioned whether CR has retained its efficacy in the modern era. Moreover, these trials typically enrolled predominately low-risk, middle-aged males following MI or PCI. Therefore, it is not clear if the results of these trials can be extrapolated to other subgroups (e.g. females, elderly, and high-risk CR patients).

To date, few studies have documented the effect of outpatient CR on survival in community-based cohorts in daily clinical practice, i.e. outside the tightly controlled setting of an RCT. Most of these studies were conducted in the USA,15–20 and were limited to subgroups of the overall population, including only Medicare beneficiaries aged 65 and older,15 dialysis patients,16 patients receiving PCI,17 patients receiving coronary artery bypass surgery (CABG),18 patients receiving combined heart valve and CABG,19 or post-MI patients.20 Outside the USA, Alter et al.21 and Martin et al.22 reported the effect of CR on survival in Canada; Beauchamp et al.23 reported the effect of attendance at CR on survival in Australia; and Lewinter et al.24 reported the effect of referral for CR (irrespective of participation) on survival in the UK. These studies, however, were limited to a single CR program, city, hospital, or county, respectively.

The objective of this study was to estimate the effect of CR in the full population and across the entire spectrum of acute indications for CR, using a large health insurance claims database in the Netherlands. Responding to the call for incorporating the impact of patient characteristics,25 we report the effect of CR stratified by age, gender, and cardiac diagnosis/intervention. We hypothesized that CR in the Netherlands is associated with a survival benefit in the full population across all strata.

Methods

Cohort selection

The cohort consisted of 3.7 million persons insured for any period between 1 January 2007 and 1 June 2010, with ‘Achmea Zorg en Gezondheid’, a Dutch health insurance firm covering ~22% of the Dutch population. The population insured with Achmea includes people from all age categories and from both urban and rural areas, and has shown to be representative of the full Dutch population with respect to the prevalence of cardiac surgery and PCI.4

We identified patients eligible for CR based on insurance claims for hospital admissions or consultations related to ACS or cardiac interventions (CABG, PCI, valve surgery). In the Netherlands, these claims are filed according to a national diagnosis-treatment classification (DTC) system based on a combination of the hospital registration of diagnoses [International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) codes] and applied therapeutic interventions. We considered only those events for which the patient was alive and insured with Achmea for a 365-day period prior to, and during a 180-day period following the starting date of the event. Each patient was included in the study only once, with the inclusion date determined by the occurrence of the diagnosis or intervention with the highest expected CR uptake rate according to a prioritization algorithm that was defined in previous research.6 Specifically, we first selected all patients who underwent one of the following interventions during the study period (in this order): CABG, valvular surgery, PCI acute, and PCI elective. Each patient was retrieved only once. Secondly, for patients who underwent CABG, valvular surgery, or PCI, we linked one of the following diagnoses (established in the previous 12 months) to these interventions (in this order): ST-elevation MI (STEMI), non-STEMI, unstable angina pectoris (AP), stable AP, and chronic heart failure (CHF). If no diagnosis was found, patients were retained in the study data set without listed diagnosis. Finally, the database was searched again, selecting from the remaining patients those with the following diagnoses during the study period (in this order): STEMI, non-STEMI, or unstable AP. These groups include patients who did not undergo one of the aforementioned interventions during the study period.

Treatment

In the Netherlands, it is mandatory to have health insurance. Reimbursement for outpatient CR after an ACS or cardiac intervention is provided by all insurance companies on the condition that a patient is referred by a cardiologist. Patients entering outpatient CR in The Netherlands are offered a comprehensive multi-disciplinary rehabilitation programme with a typical duration of 6–12 weeks, consisting of one or more group-based therapies (education, exercise training, relaxation therapy, and lifestyle modification therapy) supplemented by individual counselling when indicated (e.g. by a psychologist, dietician, or social worker). Consistent with international guidelines the Dutch guidelines for CR state25 that the individualized programme should be based on a needs assessment procedure where data items concerning the patient’s physical and psychosocial condition are gathered. In general, 85% of the patients receive exercise training, 75% receive education, 39% receive relaxation therapy, and 17% receive lifestyle modification therapy.26

Concerning exercise training, there is no fixed volume of training hours in these programmes, as baseline aerobic exercise capacity and personal and training goals vary from patient to patient. However, programmes typically last 8–12 weeks during which patients attend two training sessions per week and training intensity is generally based on maximal heart rate which is determined by symptom limited exercise testing. Dutch CR guidelines recommend that training intensity should commence on a moderate intensity level with a gradual increase until the final intensity level in 1–2 weeks. According to a recent survey study27 among Dutch CR centres, exercise training consists of aerobic training and strength training in the vast majority of the centres with a mean frequency of 2.3 per week, a session duration of 30 min and a total training volume of 6.7 h in post-ACS patients. The mean intensity of aerobic training in this group was 65% of maximal heart rate. Education therapy in Dutch CR centres is usually organized in four group sessions provided by a cardiologist, a dietician, a psychologist or social worker, and a physical therapist. A relaxation therapy program is generally based on the principles outlined by van Dixhoorn et al.28 and typically consists of 4–6 sessions lasting 60–90 min. A lifestyle modification therapy program comprises individual screening and four group sessions, focusing on cognitive aspects of lifestyle behaviour (e.g. stress management, dietary habits, exercise behaviour, and smoking cessation). In addition to these group therapies, patients may be referred for individual treatment when needed (e.g. to a psychologist, dietician, or smoking cessation program). Specialized rehabilitation centres in the Netherlands typically offer nutritional counselling by a clinical dietician to patients with overweight, hypertension, diabetes, or hypercholesterolaemia. Patients are sometimes referred to these specialized rehabilitation centres when their own hospital does not offer this service.
In the present study, consistent with previous observational studies, patients were classified as having received CR when a claim was filed for at least one of the group-based outpatient treatments. Treatment status (CR vs. no CR) was determined between study inclusion and a 180-day landmark (i.e., during a 180-day period following the ACS or the cardiac intervention). Patients were excluded if they started CR prior to the inclusion date, more than 180 days after the inclusion date, or both.

Outcome
Survival time (in days) from the inclusion date onward was our main outcome, limited to a total follow-up period of 4 years, with a minimum of 180 days (the landmark period). For all patients who switched to another insurer during the study period or were alive at the end of the study period, survival status was unobserved (right-censored).

Confounders
We included six categories of potential confounders, all measured during the 365-day period up to (and including) the study inclusion date. The first five categories comprise variables which we expected a priori to be a potential confounder: (a) age and gender; (b) cardiac diagnoses and interventions recorded during hospital visits and admissions; (c) outpatient cardiac medication prescriptions; (d) co-morbid conditions derived from hospital diagnoses (part of the DTC system) and outpatient prescriptions; (e) total healthcare expenditure; the sixth category (f), included any other characteristics associated with survival, observed from the data, without a specific a priori expectation on its status as a confounder.

For this latter category, we examined all available information in the data, comprising hospital diagnoses-treatment combinations (DTC), outpatient prescriptions based on the hierarchical Anatomical Therapeutic Chemical (ATC) classification, and medical devices, the occurrence of lab tests, GP visits, intensive care unit (ICU) days, and other services not covered by the DTC system, to construct a large set of (proxies for) potential confounders [Whereas these characteristics all applied to the year before the inclusion date, we also added diagnoses and treatments occurring at the inclusion date. All variables occurred twice in the data, coded as ‘at least 1’ (0/1 indicator) and as the actual amount/quantity]. Because many of these characteristics applied to small groups of patients, lacking statistical power at this most detailed level, we added indicator variables aggregated across various dimensions. Specifically, we added aggregated variables for diagnoses, grouped diagnoses, treatments, grouped treatments, physician specialty, and 3-digit ATC prescription groups. Physician specialty and (grouped) diagnoses were interacted with being hospitalized (vs. outpatient care) in separate variables.

From this large set, confounders with a prevalence <100 or perfect correlation with treatment, outcome, or both, were excluded from the analysis. When two confounders had perfect correlation, only one was included in the analysis.

Statistical method
To estimate the effect of CR on survival, while controlling for potential confounders, we used a three-step approach. First, we aimed to select, from the six categories of confounders described in the previous section, a parsimonious set of variables related to the outcome of interest (survival time), using an automated variable selection method known as the lasso. Secondly, we applied inverse propensity score weighting to yield a most conservative estimate of the effect of CR on survival, adjusting for both confounders preceding or occurring concurrent in time with CR treatment and any immediate effects of CR on downstream utilization.

We carried out sensitivity analyses to evaluate the robustness of our main result. First, we changed the landmark period from 180 to 90 days, and repeated the analyses. Secondly, we used conditioning rather than propensity score weighting to control for potential confounders in the Cox proportional hazards regression. All analyses were performed using SAS Version 9.1 (SAS, Cary, NC, USA) and R version 2.15.2 using the R packages glmnet, twang, and survival.

Results
We identified 38 369 patients eligible for CR during the period 1 January 2007–3 June 2010 (24 014 with at least one of the interventions CABG, valve surgery, or PCI; and 14 355 with an acute coronary syndrome [MI or unstable AP]), continuously insured with Achmea during a period starting 365 days before the event and ending 180 days thereafter (see Figure 1 for patient flow). We excluded 2450 patients because of the following reasons: initiation of CR during the year before the inclusion date (1312 patients); initiation of CR more than 180 days after the inclusion date (556); unknown gender (6); initiation of inpatient cardiac rehabilitation within 1 year after the inclusion date (635); or censored within 10 days of follow-up (23).

The final study population included 35 919 patients. The mean age of the population was 66.7 years and the majority was male (63.5 percent). Medication use and comorbid conditions in the treatment and control groups are listed in Table 1.

Out of a total of 919 potential confounders, 99 remained after applying automated variable selection (details on these results and methodology are provided in Supplementary material online, Technical Appendix). Of these 99 variables, we show a subset of 26 in Table 1 (a table including all 99 variables is added as a Supplementary material online, Appendix). Table 1 shows substantial and statistically significant differences between both groups (CR vs. no CR). For example, patients not receiving CR were on average 4.8 years older, more likely to be female, had 1220 euro higher medical cost in the prior year, were more likely to have specific comorbid conditions and were more likely to have received specific cardiac medications, including statins and antiplatelet agents (clodigrel and aspirin). Patients receiving CR were more likely to have received CABG or
acute PCI; and were more likely to have been diagnosed with MI in the year prior to inclusion. The full set of 99 variables included indicators of underlying co-morbidities, for example hospital visits/admissions related to a heart failure diagnosis; and physical limitations, such as hospital visits/admissions to the orthopaedic, pulmonology, or neurology department, and visits of the GP to the patient’s home.

**Figure 1** Flow of participants through study.
In total, 11,014 patients (30.7%) started CR within 180 days after the inclusion date. Median follow-up (counting from the study inclusion date) was 25.2 months (min. 6 months, max. 48 months). Table 2 compares crude mortality rates between patients who received CR and those who did not receive CR. In the full cohort, the mortality rate (deaths per 1000 person-years) for the former was 12.2, more than three times lower than the mortality rate (39.6) for patients who did not receive CR. In the full cohort, patients receiving CR had a large and statistically significant treatment effect on mortality with an HR of 0.35 (95% CI 0.30-0.41). After adjusting for observable confounders through the Cox proportional hazards model, the HR remained significant (0.33; 95% CI 0.28-0.40).

After applying propensity score weighting, the characteristics shown in Table 1 are distributed evenly between both groups, with no differences being statistically significant for any variable. In the full set of 99 variables, 92 differed significantly ($P < 0.05$) without propensity score adjustment. After propensity score adjustment, two differences remained statistically significant ($P < 0.05$), less than half of the expected number to occur by chance alone, suggesting excellent balance between both groups. In the subgroup analyses, the number of statistically significant differences varied between zero (age $\leq 70$) and six (females, no ACS). Figure 2 shows, for all 99 variables, the absolute standardized difference before and after propensity score weighting. After propensity score weighting, these standardized differences are well below 10%, a threshold commonly considered to indicate sufficient balance.

Table 3 shows the effect of cardiac rehabilitation on survival, estimated through the Cox proportional hazards model, after propensity score weighting to adjust for observable confounders. In the full cohort, patients receiving CR had a large and statistically significant effect on survival with a HR of 0.33 (95% CI 0.28-0.40). After adjusting for observable confounders through the Cox proportional hazards model, the HR remained significant (0.33; 95% CI 0.28-0.40).
significant survival benefit [hazard ratio (HR) = 0.65, 95% CI 0.56–0.77] compared with patients not receiving CR, over the full (48 months) follow-up period. For shorter follow-up periods the effect was larger (HR = 0.5, 95% CI 0.37–0.67), which is an indication that the assumption of proportional hazards did not hold. Specifically, when testing for constant proportionality of hazards over time, we observed a statistically significant association between the scaled Schoenfeld residuals and time. We therefore report, in Table 3, the

### Table 2  Crude death rates in full cohort and subgroups

<table>
<thead>
<tr>
<th></th>
<th>Cardiac rehabilitation</th>
<th></th>
<th>No cardiac rehabilitation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Deaths</td>
<td>n</td>
<td>Deaths/1000 person-years</td>
</tr>
<tr>
<td>Full cohort</td>
<td>35,919</td>
<td>287</td>
<td>35,919</td>
<td>11,014</td>
</tr>
<tr>
<td>Age ≤70</td>
<td>20,357</td>
<td>117</td>
<td>20,357</td>
<td>77,287</td>
</tr>
<tr>
<td>Age &gt;70</td>
<td>15,562</td>
<td>170</td>
<td>15,562</td>
<td>3,286</td>
</tr>
<tr>
<td>Male</td>
<td>22,727</td>
<td>208</td>
<td>22,727</td>
<td>8,213</td>
</tr>
<tr>
<td>Female</td>
<td>13,192</td>
<td>79</td>
<td>13,192</td>
<td>2,801</td>
</tr>
<tr>
<td>CABG/valve surgery</td>
<td>7083</td>
<td>108</td>
<td>7083</td>
<td>4,268</td>
</tr>
<tr>
<td>No CABG/valve surgery</td>
<td>28,836</td>
<td>179</td>
<td>28,836</td>
<td>6,746</td>
</tr>
<tr>
<td>ACS</td>
<td>28,195</td>
<td>206</td>
<td>28,195</td>
<td>7,954</td>
</tr>
<tr>
<td>No ACS</td>
<td>7724</td>
<td>81</td>
<td>7724</td>
<td>3,060</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CABG, coronary artery bypass graft.

**Figure 2**  Absolute standardized differences (%) for all 99 variables, before and after propensity score weighting.
Table 3 Effect of CR vs. no CR (adjusted hazard ratio) over time in full cohort and subgroups

<table>
<thead>
<tr>
<th></th>
<th>Month 6–12 Adjusted hazard ratio (95% CI)</th>
<th>Month 6–24 Adjusted hazard ratio (95% CI)</th>
<th>Month 6–48 Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full cohort</td>
<td>0.50** (0.37–0.67)</td>
<td>0.58** (0.48–0.71)</td>
<td>0.65** (0.56–0.77)</td>
</tr>
<tr>
<td>Age ≤70</td>
<td>0.48** (0.29–0.78)</td>
<td>0.52** (0.38–0.72)</td>
<td>0.60** (0.45–0.78)</td>
</tr>
<tr>
<td>Age &gt;70</td>
<td>0.50** (0.34–0.73)</td>
<td>0.63** (0.50–0.79)</td>
<td>0.68** (0.56–0.83)</td>
</tr>
<tr>
<td>Male</td>
<td>0.45** (0.31–0.64)</td>
<td>0.55** (0.44–0.70)</td>
<td>0.62** (0.51–0.74)</td>
</tr>
<tr>
<td>Female</td>
<td>0.71 (0.41–1.24)</td>
<td>0.67* (0.45–0.98)</td>
<td>0.79 (0.58–1.08)</td>
</tr>
<tr>
<td>CABG/valve surgery</td>
<td>0.43** (0.26–0.71)</td>
<td>0.54** (0.38–0.75)</td>
<td>0.55** (0.42–0.74)</td>
</tr>
<tr>
<td>No CABG/valve surgery</td>
<td>0.58** (0.40–0.84)</td>
<td>0.62** (0.49–0.79)</td>
<td>0.71** (0.58–0.86)</td>
</tr>
<tr>
<td>ACS</td>
<td>0.55** (0.39–0.77)</td>
<td>0.61** (0.48–0.76)</td>
<td>0.68** (0.57–0.82)</td>
</tr>
<tr>
<td>No ACS</td>
<td>0.42** (0.23–0.74)</td>
<td>0.52** (0.36–0.76)</td>
<td>0.57** (0.41–0.79)</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CR, cardiac rehabilitation.
All (adjusted) hazard ratios correspond to the Average Treatment effect on the Treated (ATT) of CR vs. no CR, after adjusting for confounders using doubly robust propensity score weighting.

*P < 0.05 (CR vs. no CR).
**P < 0.01 (CR vs. no CR).

Discussion

Our findings show that receiving multi-disciplinary cardiac rehabilitation in the Netherlands is associated with a substantial survival benefit in the first 4 years following an ACS or cardiac intervention. The survival benefit associated with CR was present regardless of age, type of diagnosis, type of intervention, and follow-up duration. For females, CR uptake was associated with a statistically significant survival benefit at 2 years of follow-up only.

To study the effect of medical treatments, there is a trade-off involved between internal and external validity. Randomized controlled trials typically have high internal validity because confounding is controlled for by randomization, but often lack external validity due to selection bias (e.g. when specific patient groups were underrepresented or not included) and an artificial setting. Observational designs (as used in this study) have high external validity because the study population and setting are highly representative of the real world, but confounding due to unobserved covariates cannot be controlled.
for. We think both designs can complement each other to inform health policy decisions.

The main strength of our study is that it documents the effect of modern multi-disciplinary CR in its real-world implementation, as opposed to in an idealized, tightly controlled trial setting. Secondly, while previous studies documented this effect for the USA, Canada, and Australia, this is the first study to provide such estimates for a European country. Thirdly, our cohort is representative of the full Dutch population, and includes all patients with an ACS, eligible for CR based on current guidelines. Fourthly, the size of our cohort allowed direct comparisons between subgroups, some of which are often underrepresented in clinical trials, such as women, patients with a relatively poor survival prognosis (e.g. the elderly), and those at lower risk (e.g. patients without ACS). Finally, our study stands out in methodological rigour by adjusting both for known confounders such as clinical cardiac diagnosis and intervention, prescribed medication, and co-morbidities but also for all other confounding factors that could be derived from the data.

Our estimates on the effect of CR in the community are remarkably close to the 1-year 58.5% and 5-year 33% survival benefits reported by Suaya et al.,15 for a large cohort of Medicare beneficiaries aged 65 and older, even though the inclusion year (1997) for this study predates ours by more than 10 years. They are also close to the 33% survival benefit reported by Martin et al.,22 for Canadian CR participants who completed the program (compared with those who did not participate or complete). Our estimates are smaller compared with the 46% survival benefit of CR following PCI or CABG found by Goel et al.,17 and Pack et al.,18 the 52% survival benefit of CR following combined heart valve and CABG surgery found by Goel et al.,19 the 56% survival benefit found by Witt et al.,20 for US patients receiving PCI and post-MI, respectively, and the 53% survival benefit reported by Alpert et al.,21 for Canadian patients following cardiac hospitalization. These differences are even more striking, because the magnitude of the effect in our study diminishes with longer follow-up times, and the average follow-up time in three of these studies is approximately three times longer than in our study. A possible, although speculative, explanation for these differences is that CR has not yet reached its full potential in the Netherlands in terms of quality and comprehensiveness, compared with the USA and Canada. In fact, The Dutch Health Care Inspectorate recently released a report stating that both the participation rates and the quality of Dutch cardiac rehabilitation programs are insufficient.24 Another explanation is that our approach was able to remove more bias resulting from confounders, compared with these other studies, because we systematically searched and adjusted for all variables on prior utilization independently associated with survival, instead of only adjusting for a limited set of a priori chosen variables.

Compared with estimates on the effect of CR from clinical trials, our estimates are larger. A systematic review by Heran et al.12 found a relative risk of exercise-based CR on total mortality up to 12 months of 0.82 (95% CI 0.67–1.01), and a relative risk of 0.87 (95% CI 0.75–0.99) for follow-up longer than 12 months, across a total of 33 studies. A possible explanation for the difference with our results is that these trials enrolled lower-risk patients, who might benefit less from CR, compared with the full population eligible for CR. Furthermore, this discrepancy with our study may be explained by differences in interventions that were used. As outlined, CR programs in The Netherlands generally consist of a combination of interventions (e.g. education, exercise training, relaxation therapy, lifestyle modification therapy and individual counselling by a psychologist, dietician or social worker) rather than exercise training only. Combining these different types of interventions may result in higher motivation, better self-management skills and, as a consequence, in more sustained lifestyle changes and a reduction of the risk for future cardiovascular events. In fact, a recent meta-analysis35 showed a greater survival benefit of multimodal interventions (OR 0.48) when compared with exercise-based interventions only (OR 0.62). Finally, an explanation would be the presence of unobserved confounders for which our observational design could not control.

In contrast with previous large cohort studies,15,17 we found smaller survival benefits in women, which were not longer significant at 4 years. A possible explanation for this finding may be a higher number of non-completers/dropouts among females. This would be in line with the findings by Martin et al.,22 indicating a relatively high percent of non-completers among females (approximately two-thirds) and a direct relation between CR attendance and survival. Proposed explanations for low CR attendance in women include lower referral by physicians, and less support/encouragement from healthcare personnel and spouses to participate in these programs.36 A limitation of our observational study design, using inverse propensity score weighting, is that we could not control for confounders not observable in our data, including cardiovascular risk factors, fitness status, general activity, left-ventricular function, and patient motivation. Therefore, there may be residual confounding in the association between CR and outcomes in this study. Collecting these data was not feasible, due to our retrospective design and use of administrative data. Most of the recent observational studies on the effect of CR on survival, however, did not identify cardiovascular risk factors as major confounders. Specifically, three recent observational studies on the effect of CR on survival,17–19 found no statistically significant differences between CR participants and non-participants with respect to smoking status, body-mass index (BMI), hypertension, and hypercholesterolaemia. In a fourth study,22 differences for hyperlipidaemia, and hypertension were, although statistically significant, small from a clinical perspective (<5 percentage-points on baseline rates from 60 to 70%). We suspect that this is also true for fitness status and general activity levels, as these are likely correlated with smoking and BMI. This may, however, not be true for the presence of heart failure. Whereas Goel et al.23 and Goel et al.19 reported no difference in left-ventricular ejection fraction between CR participants and non-participants, Witt et al.20 observed lower ejection fractions among CR participants. Pack et al.18 observed a higher ejection fraction among CR participants compared with non-participants and Martin et al.22 observed a higher ejection fraction among CR participants who completed the program when compared with non-completers. In our own analysis, we had no indication that left-ventricular function differed between CR participants and non-participants, for two reasons. First, we did not observe a significant difference (P = 0.7) in the number of ICD’s in the weighted control and treatment groups (12 vs. 11). As current Dutch guidelines recommend ICD implantation in all patients with symptomatic heart failure (NYHA III)
and a left-ventricular ejection fraction < 30%,
this finding suggests that there is no substantial difference in heart failure patients in both groups. Secondly, after propensity score weighting, there was no significant difference in the use of aldosterone antagonists and sulphonamides (comprising the most commonly used loop diuretics) between patients receiving CR (2.6 and 8.2%, respectively) and not receiving CR (2.4 and 8.0%, respectively). Finally, if patient motivation (to adopt a healthy lifestyle) would have had a positive effect on CR participation, our estimates reflect a combined effect of cardiac rehabilitation and motivation, rather than the isolated effect of CR alone. However, due to the nature of the definition of CR in our study (i.e. a billing code for at least one of the therapies applied in CR), patients with insufficient motivation to complete the CR program and even early dropouts were still included in the treatment group. Therefore, we believe that motivational issues did not have a substantial influence on the results of this study.

A second potential limitation is that the data we used were collected for administrative (reimbursement) purposes, rather than scientific research, and lack detail in terms of secondary diagnoses, general practice diagnoses, and laboratory test results. The definition of diseases included as covariates were based on hospital admissions that may cause some misclassification. However, registration of the data is complete, accurate, subject to extensive control and comprehensive auditing because of the economic function of the data. Thirdly, due to limitations in the data, we were not able to measure the composition of individual CR programs, to assess adherence or dropout, or to study actual reasons for patients not to participate in a CR program. Hence, our estimates might mask underlying heterogeneity and should be considered an average effect of CR as it was offered in the Netherlands between 2007 and 2010. However, patients who were referred to a CR program, but did not start the program (i.e. not even the intake) are most likely included in the control group in our study, because hospitals are not allowed to charge for services they did not provide.

A final limitation is that changes in cardiovascular medication might have occurred after the study inclusion date, and before, during or after the CR program, possibly confounding the effect estimate of CR. However, our most conservative estimate (HR 0.79), provides an estimate of the effect of CR, while controlling for such changes in medication and utilization of healthcare services occurring during the landmark period.

The substantial survival benefits documented in our study, together with the low uptake of CR in the Netherlands and elsewhere, suggest that many patients die unnecessarily due to undertreatment following a cardiac diagnosis or intervention. Strategies to improve uptake of CR include automatic referral systems, introduction of performance measures and education of both patients and health care professionals. In addition, computerized decision support has been shown to improve CR quality by increasing professional performance measures and education of both patients and health care professionals. In addition, computerized decision support has been shown to improve CR quality by increasing professional performance measures and education of both patients and health care professionals.38

The composition of individual CR programs, to assess adherence or dropout, or to study actual reasons for patients not to participate in a CR program. Hence, our estimates might mask underlying heterogeneity and should be considered an average effect of CR as it was offered in the Netherlands between 2007 and 2010. However, patients who were referred to a CR program, but did not start the program (i.e. not even the intake) are most likely included in the control group in our study, because hospitals are not allowed to charge for services they did not provide.

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In addition, computerized decision support has been shown to improve CR quality by increasing professional concordance to clinical practice guidelines.26 Future research should investigate whether these strategies indeed improve quality and uptake of CR, and whether improvements in uptake will indeed materialize into fewer deaths.

**Supplementary material**

Supplementary material is available at European Heart Journal online.


